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Common copy number variations in fifty radiosensitive cell lines

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ABSTRACT

Hypersensitivity to radiation exposure is a major challenge to radiotherapy in the treatment of cancer patients. Copy number variations (CNVs) are believed to identify genomic regions of functional significance for radiosensitivity (RS) but have yet to be systematically investigated. We used Affymetrix 6.0 SNP arrays to survey common CNVs in a cohort of 50 radiosensitive lymphoblastoid cell lines (RS-LCLs) derived from patients with undiagnosed diseases. A total of 317 CNVs that were present in at least 10% of the studied cell lines were identified. Three hundred and eight CNVs overlapped with polymorphic CNVs, 13 of which were significantly enriched in the RS-LCLs compared to the reference. The remaining 9 CNVs were novel. The majority of these enriched and novel CNVs were chromosomal gains. The dominance of the chromosomal gains over losses is inconsistent with the traditional concept of molecular basis of RS and suggests more complex genetic mechanisms for RS.

1. Introduction

Exposure of cells to ionizing radiation causes DNA damage including single-strand breaks, base damage, double-strand breaks and DNA-protein cross-links [1–2]. The majority of DNA damage can be repaired rapidly and efficiently by endogenous repairing systems. However, some individuals have compromised repairing system, and are not able to detect and/or repair DNA damage efficiently, resulting in high sensitivity to radiation-induced toxicity. A successful radiotherapy requires maximizing radiation doses to cancer cells while minimizing damage to surrounding healthy tissue [3]. The severe toxicity in radiosensitive (RS) patients limits the effective doses that can be safely given to the majority, and has become a major challenge in the treatment of cancer patients by radiotherapy.

The genetic basis of RS has been a subject of intensive studies in the past several decades. The molecular picture of RS is emerging [4–5] but remains elusive. Researchers have recognized that a large number of genes are involved in DNA repair. Those genes work in a coordinated fashion to form repair pathways that are further coordinated with other metabolic processes, such as cell cycle control, to optimize the prospects of DNA repair [6]. It has been fully appreciated that the mutations of those genes in the repair pathways are largely responsible for RS [7]. Many of those genes have been identified, including *ATR* gene involved in the DNA damage response [8], *RAD51* gene vital for repair by homologous recombination and *BLM* gene opening up the DNA helix for repair. Some of those genes were identified in RS individuals with established disorders, such as *ATM* genes in the ataxia telangiectasia, *NBN* gene in the Nijmegen breakage syndrome and *BLM* gene in the Bloom's syndrome patients [7,9–10]. However, some apparent normal persons have also been found to be highly RS, suggesting that molecular mechanisms underlying the RS are complex and beyond simple gene mutation (loss of function).

One of the plausible alternative mechanisms regulating RS is copy-number variations (CNVs). These CNVs can range in size from kilobases (kb) to megabases (Mb) that are not identifiable by conventional chromosomal banding [11]. These CNVs may convey an RS phenotype through gene dosage-mediated change of gene expression. When a CNV (deleted or duplicated region) harbors a DNA repair pathway-related gene, the CNV can affect a RS phenotype. A number of studies using genetic approaches have shown that modulating the expression levels of DNA repair genes affects the level of radiation sensitivity. Rad51, a critical component of the DNA DSB repair pathway, represents such an example. Vispe et al. demonstrated that the plasmid-mediated overexpression of Rad51 in Chinese hamster ovary decreased the radiosensitivity by increasing the homologous recombination proficiency [12]. In contrast, reduction of Rad51 expression using antisense oligonucleotides increased the radiation sensitivity of glioma cells [13].

The application of array comparative genomic hybridization (aCGH) technique has led to the discovery of a large number of pathogenic CNVs [14–16]. These disease associated CNVs have been cataloged in DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources, https://decipher.sanger.ac.uk) and ECARUCA (European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations, http://agserver01). However, this powerful technology has not been widely used in the field of RS. Although Tomoyuki Koshikawa et al. [17] have reported a focused CNV

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study between γ-radiation-sensitive SX9 cells and γ-radiation-resistant SR-1 cells, a comprehensive survey of radiosensitive CNVs is still lacking. This is largely due to the lack of high-throughput and cost-effective methods for detecting genome-level CNVs in a large radiosensitive population.

The present study surveyed common CNVs in 50 well-characterized human RS-LCLs [18] using the Affymetrix SNP 6.0 array. We identified a number of RS-associated CNVs that are either novel or significantly enriched compared to genetic variant database.

2. Results

2.1. Initial assessment of overall chromosomal stability

Five out of 50 RS-LCLs had major chromosomal abnormalities (>6 Mb deletion or duplication) that involved chr1, chr6, chr11, chr12, chr13, chr15 and chr16 (Table 1). The sizes of abnormalities varied from missing or gaining a >6 Mb segment to an entire p/q arm or a single chromosome. The remaining 45 lines had no major abnormalities. Compared to advanced cancer cell lines, these RS-LCLs were genetically relatively stable.

2.2. Copy number variations were dominated by genomic gains

Based on our assumption that the RS-associated CNVs are most likely present in multiple cell lines, we identified a total of 317 CNVs that were present in at least 10% of the cell lines (2996 gains and 512 losses across the 50 cell lines). Three hundred and eight of those CNVs (97%) overlapped with polymorphic CNVs documented in the database of genomic variants (Supplemental Table 1). Because some of the pathogenic CNVs are frequently localized within the polymorphic CNV regions, we first identified CNVs that overlapped, but significantly enriched polymorphic CNVs, and then focused on the novel CNVs, assuming that they might contain RS-associated genes.

Of the 308 overlapping CNVs, 13 CNVs were significantly enriched in the 50 RS-LCLs as compared to the polymorphic CNVs in the genomic variant database using Affymetrix GTC 4.0 software (Table 2). These CNVs were present in at least 10 of the 50 cell lines, and varied in size from 52 kb to 150 kb. Of the 13 enriched CNVs, 135 were gains and 34 were losses. Many RefSeq genes are localized within these CNVs, including LGALS9C, ZNF717 and KCNC4 (see Table 2 for full list).

Nine novel CNVs were identified, ranging from 52 kb to 163 kb (Table 3). Once again, these novel CNVs were dominated by chromosomal gains (49 gains and 2 losses) and contained 14 RefSeq genes and one miRNA. Fig. 2 is a representation of the 81 kb gain across 9 RS cell lines on 12q13.3. miR1228, NDUFA4L2, NXPH4, SHMT2, STAC3, and LRP1 are localized in this region.

2.3. Validation of CNVs by expression analysis

Taking advantage of our available miRNA profiling data from some of those RS-LCLs, we examined the expression level of miR1228 in 3 of 9 available RS-LCLs cell lines that had a chromosomal gain involved in miR1228. The results showed that the mean expression level of miR1228 in 3 RS cell lines was twice as that of 3 normal controls (Fig. 3, $p<0.01$). The data indirectly confirmed the 81 kb gain on 12q13.3 as shown in Fig. 2.

3. Discussion

This is the first study describing the use of Affymetrix SNP6.0 arrays for detection of RS associated CNVs in a large RS population. Results showed that these RS cell lines with unknown etiology were relatively stable with only a few major chromosomal abnormalities among the studied cell lines. Thirteen out of 317 identified CNVs were significantly enriched in the RS-LCLs compared to the naturally occurring CNVs. We also identified 9 CNVs that were present in >=10% of the 50 RS-LCLs and have not been reported in the genomic variant database, thus representing novel CNVs. Multiple RefSeq genes including retinoic acid receptor alpha within those CNV regions warrant further investigation.

The RS-associated CNVs were dominated by chromosomal gains, accounting for 80% of the enriched CNVs, and 96% of the novel CNVs. Our data suggested a possible mechanism that the genes localized at these duplicated regions negatively regulate those involved in detecting and/or repairing DNA damage. One such example is miR1228, which is localized within the 81 kb duplicated region on 12q13.3, and targets two critical DNA repair genes, TP53 and UBE2B. We are investigating if the increased expression of miR1228, as confirmed by miRNA array data, can negatively regulate the expression of those target genes, which then lead to compromised DNA repair and increased sensitivity to ionizing radiation.

The chromosomal gains can also affect the function of the DNA repair genes through other mechanisms. We detected a 52 kb amplification on 17q21.2, which includes the retinoic acid receptor alpha (RARA). We speculated that the chromosomal gain will increase the expression of RARA, and subsequently enhance RARA interactions with CDK7, PARP1 and TDG. If the above can be confirmed, the "unexpected" increase of protein–protein interactions with these potential DNA repair molecules can disturb the biological balance and act like a dominant-negative complex to interfere with the normal DNA repair functions.

A significantly enriched 52 kb CNV on 17p11.2 was the only abnormality dominated by deletion (31 cell lines with deletion and only 2 lines with duplication). LGALS9C is localized at this region. This gene encodes a predicted protein of the same size as and highly similar sequence to galectin 9. The function of this gene has not yet been established. Whether this gene has a DNA repair related function is under investigation.

Many other genes localized within the duplicated regions have either unknown function or functions that do not appear to be related to RS. This study provides a basis for functional evaluation of these genes in relation to RS. It is also important to remember that some DNA repair related genes are adjacent to or overlap with polymorphic CNVs based on the assembly hg18/b36 of the human genome. Given the inaccurate genomic coordinates of the assembly hg18/b36, the positions of these genes relative to the CNVs could change based on the assembly hg19/b37. In fact, the DNA repair gene, POLE, 100% overlapped with polymorphic CNVs based on hg18/b36, but the build hg19/b37 gave a new coordinates (133263945–133200347), which do not overlap with any polymorphic CNV.

Table 1
Major abnormalities detected in the 50 radiosensitive cell lines (>6 Mb deletion or duplication).

Cell line name	Copy number state	Loss/gain	Chr	Cytoband	Size (kb)
RS23	1	Loss	1	Entire p arm	
	1	Loss	6	Entire chromosome	
	1	Loss	16	Entire q arm	
	3	Gain	13	q22.3–q34	36,992
RS42	3	Gain	1	q23.3–q44	85,735
RS54	1	Loss	1	q43–q44	6786
	1	Loss	11	q22.1–q23.3	13,075
	3	Gain	12	q13.11–q24.33	85,119
RS56	4	Gain	15	Entire chromosome	
RS82	1	Loss	x	p21.1–p22.33	34,830

Table 2
Significantly enriched CNVs detected in the 50 radiosensitive cell lines.

Chrom	Start	Stop	Cytoband	Total Amp	Samples with Amp	Total Del	Samples with Del	Length (bps)	Overlapping genes	% of aber	% of CNV
17	18301042	18352965	17p11.2	2	RS52, 15-RS56	31	RS6, RS61, RS64, RS66, RS14, RS15, RS17, RS20, A RS-07, A RS-23, A RS-68, B-28, B-32, B-36, B-37, B-42, B-60, B-70, B-72, B-73, B-74, B-81, C RS-02, C RS-04, C RS-22, C RS-48, C RS-51, C RS-57, C RS-76, C RS-77, RS63	51,924	LGALS9C	66%	17%
11	71101690	71155917	11q13.4	18	RS52, A RS-29, A RS-50, A RS-68, B-32, B-36, B-37, B-42, B-60, B-72, B-73, B-74, B-79, B-80, B-81, B-82, C RS-25, C RS-51	0		54,228		36%	1%
7	72039040	72096486	7q11.23	13	RS52, RS17, A RS-54, A RS-68, B-37, B-42, B-70, B-73, B-74, B-79, B-80, B-81, B-82	0		57,447	NSUN5P2, TRIM74, POM121	26%	2%
3	75844047	75984649	3p12.3	13	RS17, RS20, A RS-68, B-32, B-37, B-42, B-60, B-73, B-74, B-79, B-81, B-82, C RS-25	0		140,603	ZNF717	24%	4%
4	4123182	4186066	4p16.2	11	RS6, RS52, A RS-29, A RS-54, A RS-68, B-36, B-37, B-70, B-72, B-74, B-81	0		62,885		22%	1%
4	1.2E + 08	119814322	4q26	11	A RS-07, B-28, B-32, B-37, B-42, B-60, B-73, B-74, B-81, B-82, C RS-25	0		10,0701		22%	1%
15	28400182	28486739	15q13.2	9	RS56, RS66, RS20, A RS-68, B-36, B-81, B-82, C RS-67, RS63	2	B-28, C RS-76	86,558	CHRFAM7A	22%	4%
1	1.11E + 08	110580437	1p13.3	10	RS6, RS31, RS52, RS56, RS61, RS65, RS14, RS15, RS17, RS18	0		55,143	KCNC4, SLC6A17	20%	1%
3	13625284	13683037	3p25.1	10	RS6, RS52, RS61, RS65, RS14, RS17, RS18, RS20, A RS-68, B-70	0		57,754		20%	1%
5	249197	306552	5p15.33	9	RS52, RS64, RS17, RS18, A RS-68, B-70, C RS-67, RS08, RS63	1		57,356	CCDC127, SDHA	20%	1%
5	306552	456560	5p15.33	10	RS52, RS64, RS14, RS17, RS18, A RS-68, B-70, C RS-67, RS08, RS63	0		150,009	PDCD6, SDHA, AHRR	20%	1%
16	508928	582622	16p13.3	10	RS47, RS52, RS14, RS15, RS17, RS18, A RS-68, B-70, C RS-25, RS08	0		73,695	LINC00235, C16orf11, NHLRC4, PIGQ, SOLH, RAB40C	20%	4%
17	16596541	16681617	17p11.2	10	RS52, RS17, A RS-23, B-32, B-36, B-37, B-74, C RS-51, C RS-57, RS63	0		85,077	FAM106CP, USP32P1, KRT16P2, CCDC144A	20%	2%

Note: To identify the significantly enriched CNVs, we first calculated the percentage of the number of cell lines with the specific CNV in the studied population and public database, respectively, then performed two-percentage *T*-test. If the p value was <0.01, the CNV in the studied population was considered as significantly enriched. The table was sorted based on the sum of the number of amplifications and deletions.

Table 3
Novel CNVs detected in the 50 radiosensitive cell lines.

Chrom	Start	Stop	Cytoband	Total Amp	Samples with Amp	Total Del	Samples with Del	Length (bps)	Overlapping Features
12	55851671	55933168	12q13.3	9	RS52, RS65, RS12, RS17, A RS-54, A RS-68, B-70, B-72, RS63	0		81,498	MIR1228, NDUFA4L2, NXPH4, SHMT2, STAC3, 51.20% of LRP1
17	35734619	35787071	17q21.2	6	RS52, RS17, A RS-68, B-36, B-79, RS63	0		52,453	GJD3, RARA
19	4978508	5043735	19p13.3	5	RS52, RS17, RS18, A RS-68, B-73	1	C RS-67	65,228	Contained within KDM4B
7	2845814	2947815	7p22.2	5	RS52, RS17, A RS-68, B-70, C RS-67	0		10,2002	34.82% of CARD11, 4.58% of GNA12
12	63222301	63275531	12q14.2	5	RS52, RS17, A RS-54, A RS-68, B-73	0		53,231	Region ends 15029 bp before RASSF3
19	5043735	5121724	19p13.3	5	RS52, RS17, RS18, A RS-68, B-73	0		77,990	Region overlaps with 78.05% of KDM4B
19	5121724	5285455	19p13.3	5	RS52, RS17, RS18, A RS-68, B-73	0		163,732	Region overlaps with 78.75% of PTPRS
19	52253908	52360202	19q13.32	5	RS52, RS17, A RS-68, B-70, C RS-77	0		106,295	ZC3H4, 32.22% of SAE1
22	47609092	47661828	22q13.32	4	RS52, RS17, A RS-68, B-70	1		52,737	Region starts 75341 bp after FAM19A5

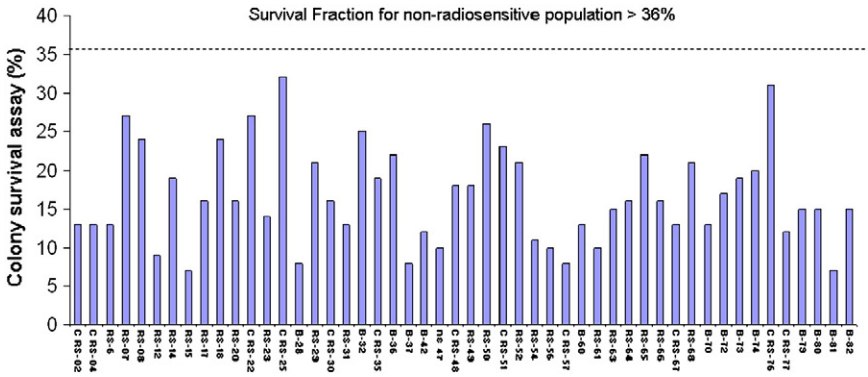

Fig. 1. The radiosensitivity of the 50 RS-LCLs measured by the colony survival assay (CSA). Normal range: >36%, intermediate radiosensitive range: 21–36%, radiosensitive range: <21% [17].

In summary, the most significant finding out of this study was the dominance of chromosomal gains over losses. This finding enriched the molecular mechanisms of RS. Our data suggest that the gene duplications through chromosomal gain may be an important, yet underappreciated, pathway in regulating radiosensitive phenotype.

4. Methods and methods

4.1. Cell lines

The 50 RS-LCLs used in this study were derived from patients with undiagnosed diseases [19]. Fig. 1 showed the radiosensitivity of these 50 RS-LCLs measured by the colony survival assay [20]. The diagnostic analyses established that they were free of any well established RS syndromes such as A-T, NBS, MRE11 and DNA ligase [21]. Fifty such RS-LCLs with unknown etiology were used in this study.

4.2. Affymetrix SNP6.0 array hybridization

Genomic DNA was extracted using standard procedures. SNP6.0 hybridization targets were prepared following manufacture's instruction. Briefly, 500 ng of genomic DNA was digested with the restriction enzymes NspI and StyI (New England Biolabs, Ipswich, MA, USA). After digestion, an adaptor was ligated to the restricted fragments, which were then PCR-amplified. PCR products were purified, fragmented, end labeled, and then hybridized for 16–18 h to the Affymetrix 6.0

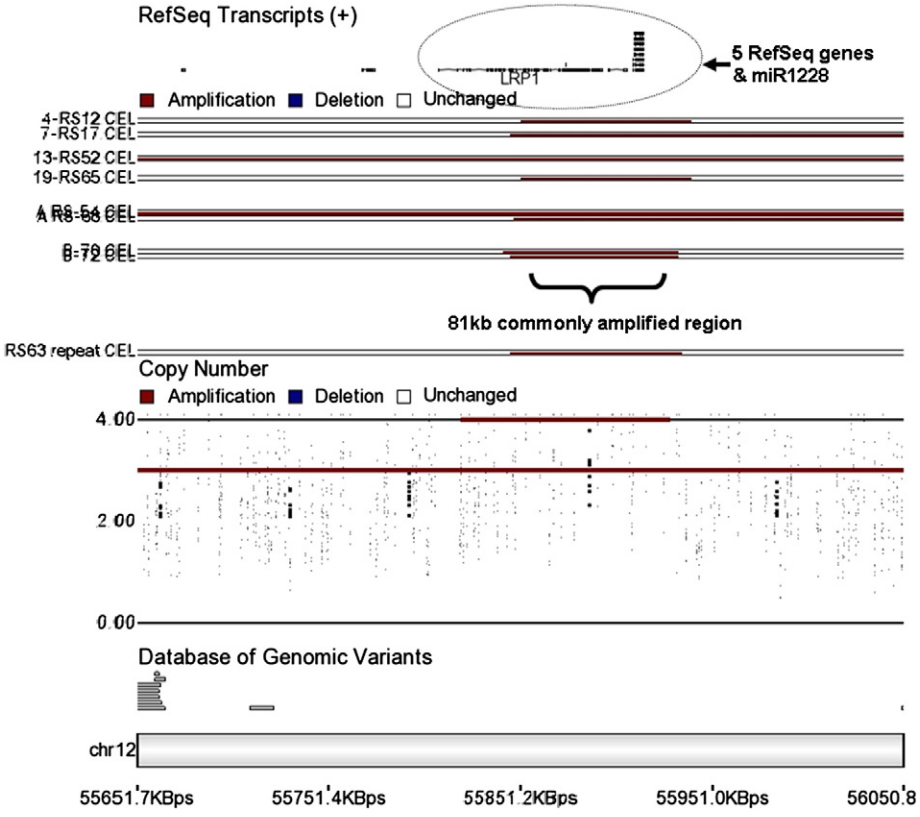

Fig. 2. A common 81 kb gain on 12q13.3 was observed in nine RS-LCLs (See Table 3 for the 9 lines). This region overlapped with 5 RefSeq genes and miRNA1228. No polymorphic CNVs have been reported in this region.

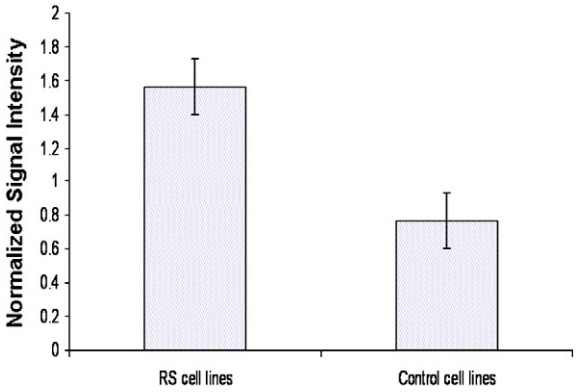

Fig. 3. A comparison of miR1228 expression by QRT-PCR between 3 RS cell lines with 81 kb gain (RS12, RS52 and RS54) and 3 normal control (NAT8, CHOC6 and ESW-1). Y axis represents normalized signal intensity. Data are expressed as mean ± SD, $p<0.01$.

chip at 49 °C in a GeneChip Hybridization Oven 640. The chips were washed, stained in GeneChip Fluidic Station 450 and scanned with Affymetrix 3000 7G scanner. Array quality was evaluated by using Affymetrix GTC 4.0 software. Only arrays with contract QC >= 0.4 and MAPD <= 0.4 were accepted for further data analysis as per manufacturer's instructions (Affymetrix, Santa Clara, CA). The analysis was based on the assembly hg18/b36 of the human genome.

4.3. Data analysis

The CEL files were imported into Partek Genomics Suite 6.0 for copy number analysis. The Affy_SNP6_baseline_794Hapmap3_122409.cnmodels (provided by Partek) was used as reference. We used genomic segmentation method for detecting amplifications and deletions. The segmentation parameters were set at the minimum genomic markers = 10 and p <= 0.001. The region list parameters were set at >=50 kb in size and >=10 markers within the 50 kb in at least 5 samples (10% tested samples). The genes and polymorphic CNVs overlapped with these regions were reported using Find Overlapping Genes tool. The CNVs on the x and y chromosomes were not included in this analysis.

4.4. miRNA array hybridization and data analysis

Total RNA from cultured cells was extracted by the Qiagen miRNeasy mini kit. One microgram of total RNA was labeled using Exiqon miRCURY LNA™ microRNA Power Labeling Kits. The labeled miRNA was hybridized to Exiqon miRCURY LNA™ microRNA Array, v. 11.0. The miRNA arrays were scanned using Axon GenePix 4000B scanner (Axon Instruments, Foster City, CA) and the images were processed using the GenePix Pro 6.1 software (Axon Instruments). The raw data were normalized by using a set of invariant endogenous miRNAs before comparison.

Supplementary materials related to this article can be found online at doi:10.1016/j.ygeno.2011.11.001.

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